PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 022-2003 WO1	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/DK 03/00463	International filing date *(day/month/year)* 02.07.2003	Priority date *(day/month/year)* 04.07.2002
International Patent Classification (IPC) or both national classification and IPC C07K14/575		
Applicant ZEALAND PHARMA A/S et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04.02.2004	20.09.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer van Heusden, M Telephone No. +49 89 2399-8145

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK 03/00463

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-43 as originally filed

Claims, Numbers

1-78 as originally filed

Drawings, Sheets

1/8-8/8 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-78
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-78
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-78 (?)
	No:	Claims	

2. Citations and explanations

see separate sheet

Additional remarks to section V:

1. Novelty and Inventive step (Article 33(2) and (3) PCT)

1.1 The present application discloses a method for the treatment of diabetes comprising administering GLP-1 or a related molecule, characterized in that the amount and timing of administration includes a so-called 'drug-holiday' during which said GLP-1 or related molecule is reduced or absent. Said method appears to be based on the finding that the GLP-1 analog (compound 1), when administered for 40 days, has a sustained effect after the administration of the compound is stopped (Figures 5-8).

1.2 The documents mentioned in this report are numbered as in the International Search Report (ISR), i.e. D1 corresponds to the first document of the ISR etc.

1.3 The GLP-1 and related molecules are known in the art and so is their use in the treatment of diabetes (all cited documents). The compound used in the examples of the present application (designated compound 1) seems to correspond to the compound represented by SEQ ID NO: 93 in document D4 (designated compound 2 in D4) and is thus also known in the art. None of the cited prior art documents discloses the concept of 'drug holidays', i.e. of reducing/stopping the administration of the GLP-1 drug for a certain time interval during the therapy. None of the cited documents discloses the sustained effect of GLP-1 on glucose metabolism and pancreatic expression of insulin. Therefore the concept of reducing/abolishing administration of the compound at intervals ('drug holidays') appears to be inventive.

1.4 In the present application the effect of compound 1 is shown to last for 40 days after stopping administration of the compound (Figures 5-8). It is noted, however, that in D4 the effect of compound 2 (corresponding to compound 1 of the present application) is shown to last for about 18 hours (see Figure 8 and p. 60). Therefore it is questioned whether the subject matter of the present claims is enabled over the entire breadth covered by the claims. It seems that the timing of drug administration/reduction is essential to achieving the sustained effect of the compound. Furthermore, due to the known instability of GLP-1 (see e.g. documents D1, D4, D9, D10) it is questioned wether said sustained effect can be achieved with any GLP-1 analog or with GLP-1 itself. Thus it appears that the present claims lack clarity under Article 6 PCT in that the essential technical

features (compound, amount and timing of administration) are not clearly defined in the claims.

2. Industrial applicability (Article 33(4) PCT)

2.1 The subject matter of claims 1-39 relates to methods of treatment of the human or animal body and is thus excluded from examination by Article 34(4)(a)(i) PCT in combination with Rule 67(iv) PCT. For the assessment of these claims on the question whether they are industrially applicable, no unified criteria exist in PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment. The applicant is already informed that in the case of a European application, claims 1-39 are not allowable because 'methods of treatment of human or animal body by surgery or by therapy and diagnostic methods practised on the human or animal body shall not be regarded as inventions which are susceptible of industrial application'.

2.2 With regard to the subject matter of claims 40-78, in the case of a European application it is not clear, in view of the present jurisdiction, whether the feature of 'amount and timing of administration' is to be considered a non-commercial and non-industrial medical activity, excluded by the EPC, or whether it could be considered to represent a further medical indication from which novelty could be derived. This question is deferred to the possible European phase.